Dyspepsia: Test and treat for *H pylori* or start PPIs?

Start empiric PPIs. **In patients with undifferentiated dyspepsia symptoms (epigastric pain with or without heartburn but without a specific diagnosis), empiric acid suppression (omeprazole 20 mg daily for 1 month) and testing for and treating *Helicobacter pylori* infection had similar results.**

The percentage of patients who were symptom free at 1 year was similar between the 2 groups. Increased costs of testing were offset by decreased costs in subsequent testing and procedures.

Delaney BC, Qume M, Moayyedi P, et al. *Helicobacter pylori* test and treat versus proton pump inhibitor in initial management of dyspepsia in primary care: multicentre randomised controlled trial (MRC-CUBE trial). *BMJ*. 2008;336:651-654.

Level of evidence

1b: Individual randomized controlled trials (with narrow confidence interval)

Is it reflux? Peptic ulcer? So-called functional dyspepsia? The trend in primary care is toward empiric treatment to control symptoms, and away from a strict diagnosis in patients who have no alarm symptoms such as hematemesis.

This study enrolled 699 adults with general symptoms of epigastric pain, heartburn, or both, lasting for at least 4 weeks but without alarm symptoms. Using concealed allocation, the patients were randomly assigned to 1 of 2 intervention groups.

The test-and-treat group was tested for *H pylori* using the urea breath test; 29% had positive results and were treated with eradication therapy and 1 month of acid suppression with a low-dose proton pump inhibitor (omeprazole 20 mg daily). Patients with negative test results were treated only with acid suppression.

Patients in the empiric treatment group did not undergo testing but received the same dose and duration of acid suppression.

Using intent-to-treat analysis, the cost, percent of patients who were symptom free at the end of 12 months, and quality of life were compared. Final results were expressed as quality-adjusted life years. Data were available for 76% of patients.

Similar quality of life at 1 year

No difference was noted between the test-and-treat group and the empiric acid suppression group, in number of patients with symptoms at 1 year, quality of life, or costs. The increased initial cost of *H pylori* testing was offset by decreases in costs incurred by other imaging.

STUDY DETAILS

Design
Randomized controlled trial (single-blinded)

Funding
Government

Allocation
Concealed

Setting
Outpatient (primary care)

FAST TRACK

No difference was noted between the 2 groups, in freedom from symptoms at 1 year, quality of life, or cost

Oral or IV steroids for inpatient COPD?

Oral steroids are as effective as intravenous (IV) steroids for nonsevere exacerbations of chronic obstructive pulmonary disease (COPD). Because oral steroids are cheaper and less invasive, they are preferred.

de Jong YP, Uil SM, Grotjohan HP, Postma DS, Kerstjens HA, van den Berg JW. Oral or IV prednisolone in the treatment of COPD exacerbations: a randomized, controlled, double-blind study. *Chest*. 2007;132:1741-1747.

Level of evidence

1b: Individual randomized controlled trials (with narrow confidence interval)

Although the oral bioavailability of corticosteroids is excellent, many physicians persist in using IV steroids for patients with exacerbations of COPD.

In this study, 210 hospitalized adults older than 40 years with COPD and at least 24 hours of exacerbation were randomized to receive 5 days of oral or IV prednisolone (60 mg daily) followed by a tapering oral dose. Patients with a severe exacerbation (pH <7.26 or $PaCO_2$ >9.3 kPa) were excluded. Allocation was concealed and patients were randomized using a "minimization protocol" that balances groups for key variables such as age, sex, smoking history, and supplemental oxygen use.

The primary outcome was treatment failure, defined as death, admission to the intensive care unit, readmission, or the need to intensify treatment. Groups were balanced at the start of the study, and analysis was by intent to treat; withdrawals and exclusions were uncommon and similar between groups.

No difference was noted between groups in the primary outcome either early (ie, within 2 weeks), late (ie, after 2 weeks), or overall. The treatment failure rate was relatively high in both groups, usually because of the need to intensify treatment.

STUDY DETAILS

Design
Randomized controlled trial (double-blinded)

Funding
Unknown/not stated

Setting
Inpatient (any location)

FAST TRACK

Oral steroids are cheaper and less invasive, and should be favored over IV steroids for nonsevere exacerbations of COPD

Do risks of hormone therapy persist after discontinuation?

No. This analysis of continued health outcomes 3 years after stopping hormone replacement therapy (HRT) in the active treatment group of the Women's Health Initiative (WHI) no longer detected a significantly increased risk of cardiovascular events or invasive breast cancer compared with the control group during the postintervention phase. The initial benefit of HRT for reducing fracture risk was also no longer observed after stopping therapy. All-cause mortality risk continued to be not significantly different between the 2 groups, but the overall "global index of risk versus benefit" remained higher among women who received active hormone treatment.

Heiss G, Wallace R, Anderson GL, et al; for the WHI Investigators. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA*. 2008;299:1036-1045.

Level of evidence

1b: Individual randomized controlled trials (with narrow confidence interval)

The WHI randomized 16,608 postmenopausal women with an intact

NSAIDs, Aspirin, and Warfarin)- Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Pristiq is initiated or discontinued. **Ethanol-** A clinical study has shown that desvenlafaxine does not increase the impairment of mental and motor skills caused by ethanol. However, as with all CNS-active drugs, patients should be advised to avoid alcohol consumption while taking Pristiq. **Potential for Other Drugs to Affect Desvenlafaxine-**Inhibitors of CYP3A4 (ketoconazole)- CYP3A4 is a minor pathway for the metabolism of Pristiq. Concomitant use of Pristiq with potent inhibitors of CYP3A4 may result in higher concentrations of Pristiq. Inhibitors of other CYP enzymes- Based on *in vitro* data, drugs that inhibit CYP isozymes 1A1, 1A2, 2A6, 2D6, 2C8, 2C9, 2C19, and 2E1 are not expected to have significant impact on the pharmacokinetic profile of Pristiq. **Potential for Desvenlafaxine to Affect Other Drugs-** Drugs metabolized by CYP2D6 (desipramine)- *In vitro* studies showed minimal inhibitory effect of desvenlafaxine on CYP2D6. Clinical studies have shown that desvenlafaxine does not have a clinically relevant effect on CYP2D6 metabolism at the dose of 100 mg daily. Concomitant use of desvenlafaxine with a drug metabolized by CYP2D6 can result in higher concentrations of that drug. Drugs metabolized by CYP3A4 (midazolam)- *In vitro*, desvenlafaxine does not inhibit or induce the CYP3A4 isozyme. Concomitant use of Pristiq with a drug metabolized by CYP3A4 can result in lower exposures to that drug. Drugs metabolized by CYP1A2, 2A6, 2C8, 2C9 and 2C19- *In vitro*, desvenlafaxine does not inhibit CYP1A2, 2A6, 2C8, 2C9, and 2C19 isozymes and would not be expected to affect the pharmacokinetics of drugs that are metabolized by these CYP isozymes. **P-glycoprotein Transporter-** *In vitro*, desvenlafaxine is not a substrate or an inhibitor for the P-glycoprotein transporter. The pharmacokinetics of Pristiq are unlikely to be affected by drugs that inhibit the P-glycoprotein transporter, and desvenlafaxine is not likely to affect the pharmacokinetics of drugs that are substrates of the P-glycoprotein transporter. **Electroconvulsive Therapy-**There are no clinical data establishing the risks and/or benefits of electroconvulsive therapy combined with Pristiq treatment. **USE IN SPECIFIC POPULATIONS: Pregnancy-** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Teratogenic effects – Pregnancy Category C- There are no adequate and well-controlled studies of Pristiq in pregnant women. Therefore, Pristiq should be used during pregnancy only if the potential benefits justify the potential risks. Non-teratogenic effects- Neonates exposed to SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [*see Warnings and Precautions (5.2)*]. When treating a pregnant woman with Pristiq during the third trimester, the physician should carefully consider the potential risks and benefits of treatment [*see Dosage and Administration (2.2)*]. **Labor and Delivery-** The effect of Pristiq on labor and delivery in humans is unknown. Pristiq should be used during labor and delivery only if the potential benefits justify the potential risks. **Nursing Mothers-** Desvenlafaxine (O-desmethylvenlafaxine) is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Pristiq, a decision should be made whether or not to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Only administer Pristiq to breastfeeding women if the expected benefits outweigh any possible risk. **Pediatric Use-** Safety and effectiveness in the pediatric population have not been established [*see Box Warning and Warnings and Precautions (5.1)*]. Anyone considering the use of Pristiq in a child or adolescent must balance the potential risks with the clinical need. **Geriatric Use-**Of the 3,292 patients in clinical studies with Pristiq, 5% were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. For elderly patients, possible reduced renal clearance of desvenlafaxine should be considered when determining dose [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.6) in the full prescribing information*]. **Renal Impairment-** In subjects with renal impairment the clearance of Pristiq was decreased. In subjects with severe renal impairment (24-hr CrCl < 30 mL/min) and end-stage renal disease, elimination half-lives were significantly prolonged, increasing exposures to Pristiq; therefore, dosage adjustment is recommended in these patients [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.6) in the full prescribing information*]. **Hepatic Impairment-**The mean $t_{1/2}$ changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively. No adjustment in starting dosage is necessary for patients with hepatic impairment.

OVERDOSAGE: Human Experience with Overdosage- There is limited clinical experience with desvenlafaxine succinate overdosage in humans. In premarketing clinical studies, no cases of fatal acute overdose of desvenlafaxine were reported. The adverse reactions reported within 5 days of an overdose > 600 mg that were possibly related to Pristiq included headache, vomiting, agitation, dizziness, nausea, constipation, diarrhea, dry mouth, paresthesia, and tachycardia. Desvenlafaxine (Pristiq) is the major active metabolite of venlafaxine. Overdose experience reported with venlafaxine (the parent drug of Pristiq) is presented below; the identical information can be found in the *Overdosage* section of the venlafaxine package insert. In postmarketing experience, overdose with venlafaxine (the parent drug of Pristiq) has occurred predominantly in combination with alcohol and/or other drugs. The most commonly reported events in overdosage include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported. Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher pre-existing burden of suicide risk factors than SSRI-treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage, as opposed to some characteristic(s) of venlafaxine-treated patients, is not clear. Prescriptions for Pristiq should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose. **Management of Overdosage-**Treatment should consist of those general measures employed in the management of overdosage with any SSRI/SNRI. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Induction of emesis is not recommended. Because of the moderate volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for desvenlafaxine are known. In managing an overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physicians Desk Reference (PDR®).

This brief summary is based on Pristiq Prescribing Information W10529C001, revised February 2008.

uterus, ages 50 to 79 years, to receive either conjugated equine estrogen (CEE) plus progestin (PremPro) or matched placebo (concealed allocation assignment). The original trial was stopped after 5.6 years because of concern about an increased risk of invasive breast cancer and cardiovascular events in the intervention group. These investigators reported the continued health outcomes for 95% (n=15,730) of these women 3 years after the intervention was stopped. As in the original trial, individuals masked to treatment group assignment continued to report outcomes, and analysis was by intent to treat.

The initial significantly increased risk of cardiovascular events and invasive breast cancer among women assigned to the CEE/progestin group was no longer observed during the postintervention phase. The benefit of a reduced risk of fracture with hormonal therapy was also no longer observed after the intervention. The "global index of risk versus benefit" remained essentially unchanged, maintaining a nominally significant 12% increase for women in the active treatment group. All-cause mortality rates remained similar in the active and placebo treatment groups.

STUDY DETAILS

Design
Randomized controlled trial (double-blinded)

Funding
Foundation

Allocation
Concealed

Setting
Population-based

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